Claim 20 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/08/99

International application No.
PCT/SE 99/01144

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9714686 A1	24/04/97	AU 704133 B	15/04/99
		AU 7224396 A	07/05/97
		BR 9610988 A	06/04/99
		CZ 9801193 A	16/09/98
		EP 0858451 A	19/08/98
		GB 9521231 D	00/00/00
		HU 9900028 A	28/04/99
		NO 981710 A	03/06/98
		PL 326353 A	14/09/98
		US 5883102 A	16/03/99
		AU 697282 B	01/10/98
		AU 7321796 A	22/05/97
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		GB 9614386 D	00/00/00

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(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **HOLMBERG, Christina** [SE/SE]; AstraZeneca R & D Södertälje, S-151 85 Södertälje (SE).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

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Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/022249 A1

(54) Title: NEW SELF EMULSIFYING DRUG DELIVERY SYSTEM

(57) Abstract: The present invention claims and discloses a pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprising(i) one or more NO-releasing NSAID(s);(ii) one or more surfactants, of which at least one is phospholipid;said composition forming an *in-situ* oil-in-water emulsion upon contact with gastrointestinal fluids. The composition may optionally also comprise an additional oil or semi-solid fat. Further, one or more short-chain alcohols can optionally be included in the composition. Also within the scope of the invention is a combination with a proton pump inhibitor. The pharmaceutical composition is useful in the treatment of pain and inflammation. Further within the scope of the invention is kit comprising a pharmaceutical composition according to the invention in a unit dosage form, in combination with a proton pump inhibitor, and said proton pump inhibitor is enteric coated.

NEW SELF EMULSIFYING DRUG DELIVERY SYSTEM

Field of the invention

The present invention is directed to a new pharmaceutical composition in form of an emulsion pre-concentrate, a unit dosage form comprising said composition, its use in therapy as well as a process for the preparation thereof.

Background and prior art

Non-steroidal anti-inflammatory drugs, commonly abbreviated NSAIDs, are well-known drugs for the treatment of pain and inflammation. One of the major drawbacks with NSAIDs is that they have severe gastro-intestinal side effects. Patients undergoing treatment with NSAIDs for a longer period of time, such as naproxen, often experience problems with stomach gastrointestinal side effects.

Nitrogen oxide releasing NSAID compounds (in the following NO-releasing NSAIDs), have recently been found to have an improved side-effect profile, see e.g. WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641.

NO-releasing NSAIDs are lipophilic compounds with poor aqueous solubility. They can be classified into class 2 according to the Biopharmaceutical Classification System proposed by Amidon et al. *(Pharm. Res. 12 (1995) pp. 413-420)*. Drugs of this class are characterised by low aqueous solubility but reasonably well permeability. A biopharmaceutical problem with these compounds is that their absorption from the gastro-intestinal tract (GIT) may be dissolution rate limited, resulting in poor bioavailibility upon oral administration.

WO 95/08983 discloses a self-emulsifying composition for oral administration that forms a microemulsion *in situ* when in contact with biological fluids. This composition can be characterised as a self-microemulsifying drug delivery system (SMEDDS), and comprises at least

- an active compound,
- a lipophilic phase consisting of a mixture of glycerides and fatty acid esters,
- a surface-active agent,
- a co-surfactant, and
- a hydrophilic phase, which is achieved after ingestion by the physiological liquid of the digestive medium.

The present invention distinguishes in several aspects from WO 95/08983 and other SMEDDS.

US 5 929 030 discloses pre-concentrate of a microemulsion as a suitable pharmaceutical composition for a water-insoluble pharmaceutically active substance such as cyclosporin. The composition, that forms a microemulsion, comprises a) a water-insoluble pharmaceutically active material; b) a lipophilic phase comprising a mixture of glycerides, and c) a phospholipid and another surfactant.

Whereas the compositions disclosed in WO 95/08983 and in US 5 929 030 form a microemulsion *in situ*, the compositions of the present invention form an emulsion.

EP 274 870 discloses a pharmaceutical composition comprising a non-steroidal anti-inflammatory drug (NSAID) and a surfactant, the composition being capable of forming micelles containing the NSAID upon oral administration. These micelles have been found to present a particularly appropriate form to administer NSAIDs orally, alleviating their adverse effects on the gastrointestinal tract (GIT). Micelles are aggregates in which the surfactant molecules are generally arranged in a spheroidal structure with the hydrophobic region at the core shielded, in an aqueous solution, from the water by a mantle of outer hydrophilic regions. The drug is usually solubilised in the surfactant. Micelles are to be contrasted in terms of their structure with emulsions, which are formed by compositions of the present invention. Whereas micelles are thermodynamically stable one-phase-systems (according to the Gibbs phase law) in which the aggregates usually have a diameter of

approximately two lengths of the surfactant molecule forming it, i.e. in the order of some ten to hundred Ångström (Å), emulsions are much larger aggregates, in the order of nanometers to micrometers in diameter, consisting of an oily core which is surrounded by one or several layers of surfactants. Emulsions are generally two-phase-systems, and they are thermodynamically unstable (but may be kinetically stable). Another major difference between the compositions of EP 274 870 and the present invention is the nature of the active compound. Whereas NSAIDs are crystalline powders by nature, the NO-releasing NSAIDs or mixtures of NO-releasing NSAIDs used in the present invention are in oil form or in a semisolid form. Moreover, micelles usually require a much higher drug:surfactant ratio compared to the oil:surfactant ratio required to form an emulsion.

One of the unique features with NO-releasing NSAIDs is that many of these compounds are oils or thermosoftening semisolids, which are practically insoluble in water. With high-dose NO-releasing NSAIDs, e.g. when the dose is above about 350 mg, it is difficult to formulate a tablet of reasonable size of the large amount of oil or semisolid. The lipophilic NO-releasing NSAIDs can, however, be formulated as oil-in-water emulsions where the compound constitutes, or is part of, the oil phase emulsified in water by one or more surfactants. An addition of a lipophilic solubiliser phase is not needed for the present invention since the active compound, the NO-releasing NSAID, is able to solely constitute the oil phase of the *in situ* emulsion. Further, the addition of a co-surfactant can be avoided by the present invention, i.e. the toxicological concern is reduced to a minimum.
In pharmacokinetic animal studies it has been surprisingly found that such oil-in-water emulsions of NO-releasing NSAIDs display a much better bioavailability compared to the unemulsified substance. A problem with emulsions is, however, that they are thermodynamically unstable and have poor long-term storage stability since they often tend to coalescence, creaming/sedimentation or phase separation. It is *inter alia* not possible to fill oil-in-water emulsions into gelatine capsules since the high water content of the emulsion is incompatible with the capsule shell and would dissolve it.

Outline of the invention

The problems mentioned above have now been solved by providing a novel Self Emulsifying Drug Delivery System, commonly known as SEDDS, suitable for oral administration. More particularly, the present invention is directed to a pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprising

(i) one or more NO-releasing NSAID(s);
(ii) a phospholipid optionally together with one or more other surfactants;
(iii) optionally an oil or semi-solid fat;

said composition forming an *in-situ* oil-in-water emulsion upon contact with aqueous media such as gastrointestinal fluids.

The composition according to the present invention may optionally further comprise one or more short-chain alcohols.

The composition will form an *in situ* oil-in-water emulsion of small droplets of nanometer to micron size upon contact with gastrointestinal fluids, the droplets being constituted of one or more NO-releasing NSAIDs forming the core of the droplet, which is covered by one or several layers of surfactant. The *in situ* formed oil-in-water emulsion will provide a good bioavailability of the NO-releasing NSAID upon oral administration. Storage stability of the emulsion is not a concern since the emulsion is not formed until the pre-concentrate has been taken by the patient, i.e. first at the moment of administration. The possibly unpleasant taste of the pre-concentrate is not a problem when filled into capsules.

The pharmaceutical composition according to the present invention is an emulsion pre-concentrate at the time of administration to a patient. The emulsion pre-concentrate can be filled into unit dosage forms such as capsules, drinking ampoules and dose cushions, or may alternatively be formed as other suitable dosage forms such as chewable soft pills and chewy-base lozenges.

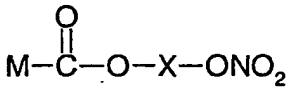
Upon contact with aqueous media such as gastrointestinal fluids, the emulsion pre-concentrate transforms into an oil-in-water emulsion. Thus, the composition will form an *in-situ* oil-in-water emulsion in the gastrointestinal tract (GI tract). The drug release rate of the composition is determined by the droplet size of the *in situ* emulsion and the polarity of the emulsion droplets, the latter being governed by the hydrophilic-lipophilic balance (HLB) of the drug/surfactant mixture, and the concentration of the surfactant. Generally, small droplet size and high polarity gives rise to a high drug release rate *(N.H. Shah et al., Int. J. Pharm. 106 (1994), pp. 15-23).*

The wording "NSAID" is defined as a non-steroidal anti-inflammatory drug, i.e. any drug having an anti-inflammatory effect, but which compound does not belong to the compound class "steroids". A person skilled in the art will know whether a compound falls under the definition NSAID. Examples of specific NSAIDs are naproxen, diclofenac, aceclofenac, indomethacine, ketorolac, sulindac, meloxicam, piroxicam, tenoxicam, ibuprofen, ketoprofen, naproxen, azapropazon, nabumetone, carprofen, tiaprofenic acid, suprofen, indoprofen, etodolac, fenoprofen, fenbufen, flurbiprofen, bermoprofen, pirazolac, zaltoprofen, nabumetone, bromfenac, ampiroxicam, and lornoxicam. This list should however not be considered as exhaustive in any way. The wording "NO-releasing NSAID" is contemplated to include any non-steroidal anti-inflammatory drug (NSAID), a salt or an enantiomer thereof, which has the capability to release nitrogen oxide.

NO-releasing NSAIDs are lipophilic compounds with poor aqueous solubility. They can be classified into class 2 according to the Biopharmaceutical Classification System proposed by *Amidon et al. (Pharm. Res. 12 (1995) 413-420)*. Drugs of this class are characterised by

low aqueous solubility but reasonably well permeability. A biopharmaceutical problem with these compounds is that their absorption from the gastro-intestinal tract (GIT) may be dissolution rate limited resulting in poor bioavailibility upon oral administration.

Preferred NO-releasing NSAIDs in accordance with the present invention, are compounds of the formula I

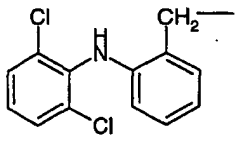


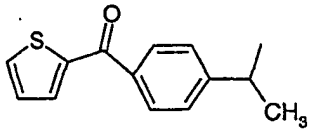
I

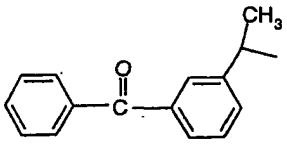
wherein

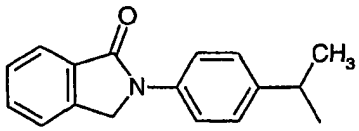
X is a spacer, i.e. a compound forming a bridge between the nitrogen oxide donating group and the NSAID; and

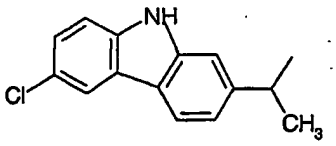
M is selected from anyone of

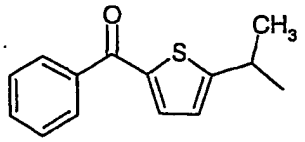


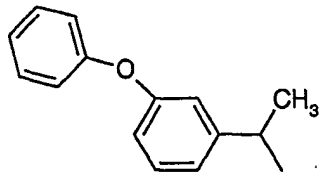


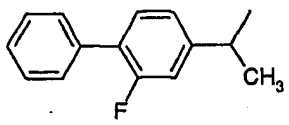


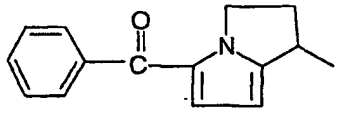


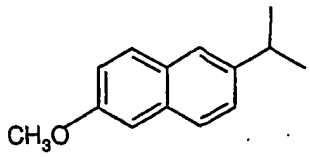


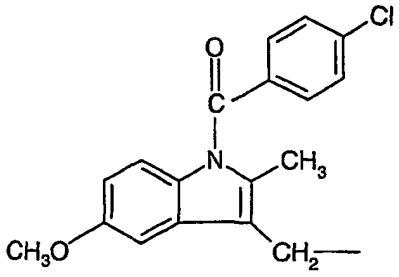


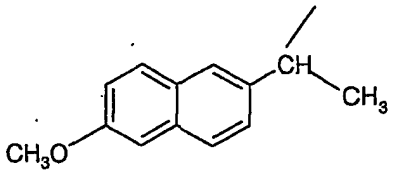


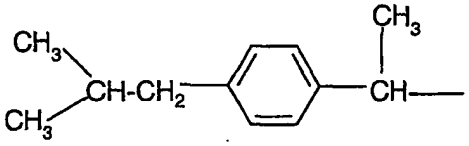












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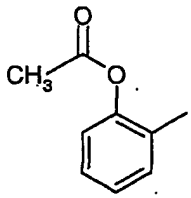
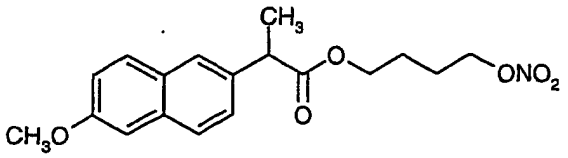


In a preferred embodiment of the invention, the spacer X is selected from a linear, branched or cyclic alkylene group $-(CH_2)-_n$ wherein n is an integer of from 2 to 10; and $-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-(CH_2)p-\ C_6H_4-CH_2-$ wherein p is an integer from 2 to 10.

In one embodiment of the invention, NO-releasing NSAIDs contemplated as active compound(s) in the SEDDS formulation according to the present invention, are compounds disclosed and claimed in WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641, which are hereby incorporated by reference.

Specific NO-releasing substances useful in accordance with the present invention are



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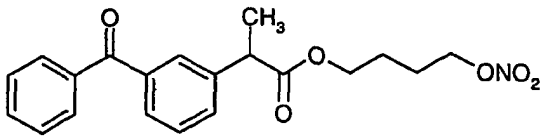

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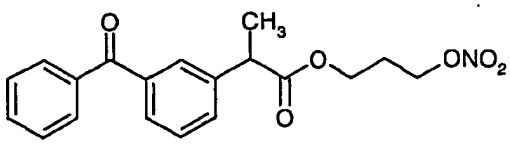

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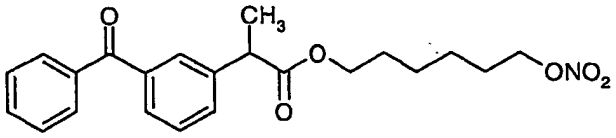

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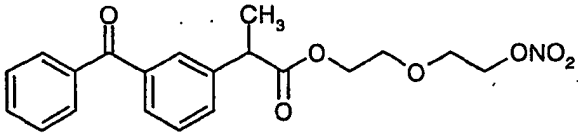

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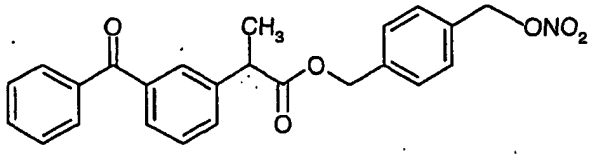

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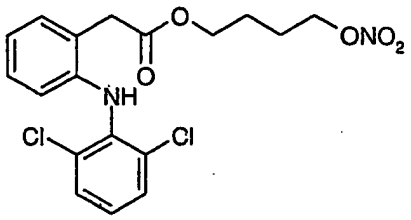

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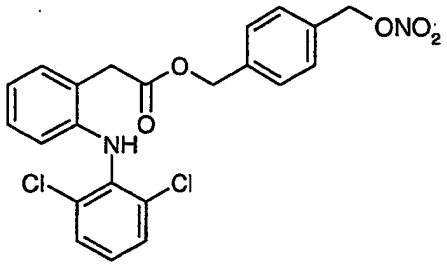

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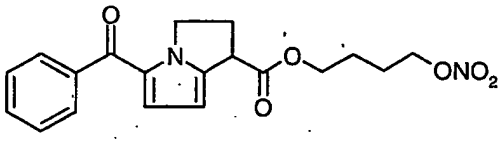

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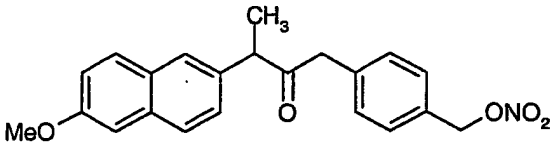

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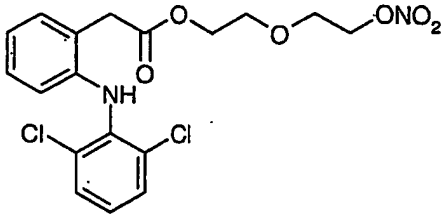

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